Amendments to the Specification

Please replace the paragraph at page 2, lines 17 through 29 with the following amended paragraph:

Fig. 2 depicts typical steps that can be included in a macromolecule sample preparation process operating on a mixture 202. If the macromolecule is endogenous, i.e., is at least partly contained in cells, an optional lysing step 204 opens the cells so that the macromolecule 104 can be separated. Separation step 206 separates macromolecule 104 from rough components 207 and fine components 213. Rough components 207 can include, for example, insoluble cells 208, cellular fragments 210, soluble molecules 212 which are larger than macromolecule 104, and the like. Fine components 213 can include salts 214 and soluble molecules 215 that are smaller than macromolecule 104, and the like. The concentration of ions such as salts and hydrogen (i.e., pH) are adjusted in step 216. In step 218, the molecule can be denatured, i.e., can be heated and/or combined with a denaturing agent 220, producing prepared macromolecule 104', which is typically at an increased concentration compared to macromolecule 104.

Please replace the paragraph at page 4, line 21 through page 5, line 2 with the following amended paragraph:

In one example of CE technology a fragile, small diameter capillary is repeatedly applied by robotics to a series of distinct inlet vials. The repetitive motion can easily break the CE column. ~~In either case, column~~ Column replacement requires time-consuming recalibration of the robotic motion. Another example of CE technology employs microchannels etched into a glass chip. While this hardware is durable, the separation efficiency is limited by the length of CE channel that can be fabricated on a chip. Attempts to extend the channel length by increasing channel density on a chip generally restrict high electric fields from use, increasing separation time. Also, the throughput of this technique is limited. Furthermore, sample transfer as practiced in both the robotic capillary technique and the chip technique expose the analytic solution to undesirable environmental contamination.

Please replace the paragraph at page 7, lines 3 through 4 with the following amended paragraph:

Fig. 7D depicts apparatus 752 ~~with a relief valve 758, overflow reservoir 760, and filter 766~~ wherein inlet and outlet valves 703 and 702 can be double isolated gate valves.

Please replace the paragraph at page 11, line 28 through page 12, line 2 with the following amended paragraph:

Fig. 7A depicts rough separation circuit 700. The liquid mixture can be drawn from bioreactor sample site 102 by opening ~~inlet~~ valves 702, 703, and 502 while closing valves 704, 706, 708, 710, 712, and 714 along the fluid stream. The line from site 102 includes a liquid/air trap region 715, including waste valve ~~712~~704, waste site 720, and flow sensor ~~714~~718.

Please replace the paragraph at page 13, lines 10 through 16 with the following amended paragraph:

Inlet valve 703 is coupled to a biofluid source site, e.g., bioreactor 102. A sampling conduit 754 extends from ~~the~~ inlet valve 703 to ~~an~~ outlet valve 702. Outlet valve 702 is coupled to a biofluid process site, e.g., the apparatus 753. Trap 715 is located at sampling conduit 754. Waste valve 704 is located at a waste conduit 756, and extends from conduit 754 to waste site 720. A wash fluid source is coupled to at least one of the inlet and outlet valves 703 or 702, e.g., as depicted, reservoir/valve 728/706 is coupled through outlet valve 702. The valves are all adapted for automatic control.

Please replace the paragraph at page 13, line 17 through page 14, line 2 with the following amended paragraph:

Trap 715 is a portion of conduit 754 that is lower in height than either end of ~~the~~ conduit 754, e.g., so that fluid in ~~the~~ conduit 754 tends to collect there under gravity. The lowest portion of the trap is generally below the lowest end of conduit754 by a multiple of the conduit internal diameter (or average internal diameter) of at least about 3 times, more typically, at least about 5 times, even more typically about 10 times and preferably at least about 20 times. The trap is typically a U-shaped portion of conduit, and the ends, e.g., at input and output valves 703 and 702, are preferably at the same height. Waste valve 704 can be coupled to any point in the trap but is typically coupled to the lowest point of the trap. The volume of the conduits bounded by valves 703, 702, and 704, e.g, the volume of the trap, in milliliters, is related to the cross-sectional area of the conduit by a multiplier that is typically less than about 15, more typically less than about 10, even more typically less than about 5, still more typically less than about 2, and preferably less than about 0.5. For example, for a conduit with a cross sectional area of 1 millimeter^2, if the factor is 10, the volume is less than about 10 milliliters; if the factor is 2, the volume is less than about 2 milliliters;[[,]] and the like.

Please replace the paragraph at page 14, lines 3 through 22 with the following amended paragraph:

Aseptic fluidic interface apparatus 752 can control fluid transfer between the two systems so that fluid is transferred in a particular direction at particular times, e.g., only from bioreactor 102 to apparatus 753 during sample collection. For example, automated controller 701 can communicate electronically with the valves, collecting fluid sample from bioreactor 102 by opening inlet valve 703, directing the sample to apparatus 752 by opening outlet valve ~~1604~~702 while waste valve 704 is closed. Reactor 102 and apparatus 753 can be isolated by closing inlet valve ~~702~~703 and outlet valve 702, and trap 715 and sampling conduit 754 can be drained to waste site 720 by opening waste valve 704. Before transferring a sample, preferably as part of each sample cycle, sampling conduit 754 can be cleaned by opening waste valve ~~720~~704 and directing a wash fluid through at least one of ~~the~~ inlet and outlet valves 703 or 702 and subsequently through ~~the~~ waste valve 704 to ~~the~~ waste site 720, e.g., from wash reservoir 728

through outlet valve 702. An optional flow sensor 718 can be located in apparatus 752, typically at sampling conduit 754 or waste conduit 756, preferably at waste conduit 756 between trap 715 and waste site 720. Flow sensor 718 can be employed by controller 701 to sense for fluid flow, particularly when the two biofluid sites, e.g., bioreactor 102 and apparatus 753, are isolated. If flow is sensed during isolation, a possible backflow condition can be indicated. As used herein, "backflow" means undesirable fluid flow in the system, e.g., due to failure of valves 703 or 702 to close, and the like. Backflow can lead to cross-contamination, loss of valuable bioreactor fluid, and the like.

Please replace the paragraph at page 15, lines 6 through 27 with the following amended paragraph:

Fig. 7C depicts an aseptic fluidic interface apparatus 752 with a relief valve 758, overflow reservoir 760, and filter ~~762~~766, all located on relief conduit 764. Flow sensor 718 can optionally be located on relief conduit 764 as shown. Relief conduit 764 extends from waste conduit 756 at a point between trap 715 and waste valve 704, and ends in fluid communication with the external environment through filter 766. Filter 766 excludes at least a portion of external contaminants from at least a portion of the relief conduit. The filter can be located anywhere between valve 758 and the distal end of conduit 764, preferably at the end as depicted in Fig. 7C. Typically, the filter is selected to exclude microorganisms and particulate contaminants, e.g., the filter excludes contaminants having a diameter greater than about 1 μm, more typically greater than about 0.5 μm, and preferably greater than about 0.2 μm. Overflow reservoir 760 can be located anywhere between valve 758 and the distal end of conduit 764, preferably between ~~the filter~~flow sensor 718 and valve 758 as depicted in Fig. 7C. Flow sensor 718, which can be located anywhere in apparatus 752, is typically at waste conduit 756 or relief conduit 764. If the overflow elements are employed, flow sensor 718 is typically at conduit 764 as shown, preferably between valve 758 and reservoir 760. A second filter 768 can be employed at conduit 764, e.g., between valve 758 and trap 715. Filter 768 is sized smaller than filter 766, i.e., excludes at least a portion of contaminants that pass through filter 766. ~~Fir~~For example,

filter 768 is typically sized to exclude particles less than about 75 % of the size excluded by filter 766, more typically, less than about 50 % of the size excluded by filter 766, an preferably, less than about 25% of the size excluded by filter 766.

Please replace the paragraph at page 16, line 28 through page 17, line 9 with the following amended paragraph:

Automated controller 701 directs wash fluid into the sampling conduit through at least one of ~~the~~ inlet and outlet valves 703 or 702, preferably outlet valve 702. A wash fluid can be one or more fluids, e.g. a gas, a vapor, a liquid, a supercritical fluid, a combination, and the like. For example, gases can include compressed air, oxygen, nitrogen, noble gases nitrous oxide, ethylene oxide, carbon dioxide, and the like; vapor can include steam or vaporized solvents; liquids can include water, aqueous solutions of buffers, antiseptics, detergents, and the like; solvents, e.g., organic solvents such as alcohols, ethers, ketones, polar aprotic solvents, and the like; and supercritical fluids can include carbon dioxide, water, and the like. Typically, the wash fluid is sterile. More than one fluid can be employed, for example, the apparatus can be flushed with an aqueous cleaning solution, steam, and then dry compressed air. Preferably, at least one wash fluid is antiseptic or sterilizing, i.e., is able to kill microorganisms.

Please replace the paragraph at page 16, lines 14 through 27 with the following amended paragraph:

Automated controller 701 is typically employed with the wash fluid to reduce bacterial count, macromolecule contamination, and/or other contamination to acceptable levels. An "acceptable level" of contamination is that level of contaminants that do not have a measurable adverse effect on the bioprocess site. For example, macromolecule contamination is typically reduced below the detection level of an analysis circuit coupled to the system. Contamination of any portion of the system can be measured using rinse water, e.g., by filling that portion with rinse water, letting stand at 20 °C for 1 minute, and then analyzing the rinse water for the

concentration of macromolecules or bacteria. Typically, washing can reduce bacterial contamination, e.g., the number of bacterial colony forming units per milliliter of rinse water to less than about 100, more typically, to less than about 50, and preferably, to less than about 10. Generally, washing can reduce macromolecule contamination in rinse water to less than about 10 parts per million (ppm), more typically, to less than about 1 ppm, even more typically, less than about 0.1 ppm, and preferably, to less than about 0.01 ppm.

Please replace the paragraph at page 16, line 28 through page 17 line 7 with the following amended paragraph:

Fig 7D depicts still other options for apparatus 752. One or more valves, e.g., ~~the~~ inlet and outlet valves 703 and 702 can be double isolated gate valves. As used herein, a double isolated gate valve is a single valve unit that can be considered as two coupled three-way valves. Typically, a double isolated gate valve has minimal dead volume between each of its three-way valves. These valves can allow other options for fluid flow. For example, wash fluid can be directed into the system through one such valve, e.g., into outlet valve 703. The wash fluid can then be directed out of the remaining output of double isolated outlet gate valve 703 to waste site 720, or alternatively, into sampling conduit 754, up to double isolated inlet gate valve ~~703~~702, and then to waste site 720.

Please replace the paragraph at page 18, lines 4 through 8 with the following amended paragraph:

Next, valves 522 and 806 close, valves 510 and 520 open[[s]], and pumps 518 and 506 work together to direct the mixture to denaturation circuit 900, where valves 902, 904, 906, and 908 are closed (see Fig. 9). Pumps 518 and 506 operate at a rate of about 1.5 mL/min. Typically, rough pump 506 will push a total of about 2.5 mL, while fine pump 518 will push a total of about 7.5 mL.

Please replace the paragraph at page 18, lines 13 through 18 with the following amended paragraph:

Fig. 9 depicts denaturation circuit 900. Denaturation vessel 526 is preferably a 10 ~~ml~~mL stainless steel vessel that contains both heating and cooling coils. The mixture can be heated until at least partial denaturation occurs, for example, heating to at least about 70 °C for about 90 seconds, or more preferably, heating to about 90 °C for about 300 seconds. Subsequently, the cooling coil can be operated to cool the sample to about 25 °C.